Summary Basis for Regulatory Action

Date: June 10, 2016

From: Goutam Sen, Ph.D., Chair of the Review Committee

BLA/STN: 125597/0

Applicant Name: PaxVax Bermuda Ltd.

Date of Submission: October 15, 2015

PDUFA Goal Date: June 15, 2016

Proprietary Name: VAXCHORA®

Established Name: Cholera Vaccine Live Oral

Indication: VAXCHORA is indicated for active immunization against disease caused by *Vibrio cholerae* serogroup O1 in adults 18 through 64 years of age traveling to cholera-affected areas.

Recommended Action: Approval

Review Office Signatory Authority: Marion F. Gruber, Ph.D.,
Director
Office of Vaccines Research and Review

√ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Office of Compliance and Biologics Quality Signatory Authority:
Mary Malarkey
Director
Office of Compliance and Biologics Quality

√ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Specific documentation used in developing the SBRA	**Reviewer name – Document(s) date**
Clinical Review	Tina Khoie Mongeau, M.D., M.P.H.– May 16, 2016
Statistical Review (Clinical effectiveness)	Sang Ahnn, Ph.D. - March 29, 2016
Clinical Serology Assay Review	Manuel Osorio, Ph.D. – March 28, 2016
CMC Review	Roger Plaut, Ph.D. – March 30, 2016 Alfred Del-Grosso, Ph.D. - April 22, 2016 Simleen Kaur, M.S. - April 5, 2016
Facilities and CMC Review	Christine Harman, Ph.D. and Deborah Trout, B.S. – March 14, 2016
Lot Release Protocol Template	Marie Anderson, Ph.D., - April 22, 2016
Bioresearch Monitoring Review	Christine Drabick, M.S. – March 29, 2016
Epidemiology/Pharmacovigilance Review	Deepa Arya, M.D., M.P.H., M.B.A. - March 31, 2016
Advertising and Promotional Labeling	Oluchi Elekwachi, Pharm. D., M.P.H. – March 3, 2016
Establishment Inspection Report	Christine Harman, PhD, Richard Heath Coats, and Scott Norris- June 7, 2016
Inspection Waiver Memos (Testing Facilities for Drug Product release testing)	Christine Harman, Ph.D. –February11, 2016
Advisory Committee Transcript	May 27, 1998
Approved Draft Labeling	N/A

1. Introduction

PaxVax Bermuda Ltd., submitted Biologics License Application (BLA) 125597/0 for licensure of Cholera Vaccine, Live, Oral. The proprietary name is VAXCHORA®. VAXCHORA is indicated for active immunization against disease caused by *Vibrio cholerae* (*V. cholerae*) serogroup O1 in adults 18 through 64 years of age who will be traveling to cholera-affected areas.

The vaccine consists of a packet of lyophilized bacterial powder (active component) and a packet of buffer (buffer component). VAXCHORA is prepared by reconstituting the buffer component in 100 mL of bottled purified water followed by adding the contents of the active component packet. The active component packet contains $4x10^8$ - $2x10^9$ colony-forming units (CFU) of strain CVD 103-HgR, *V. cholerae* serogroup O1, biotype classical, serotype Inaba. The buffer component packet contains sodium bicarbonate, sodium carbonate, ascorbic acid and lactose. The active component and buffer component packets are intended to be stored frozen (-25°C to -15°C). The shelf-life for the lyophilized bacteria is 18 months, and the shelf-life for the buffer is 24 months from the date of manufacture, when stored at -25°C to -15°C. The expiration date for the packaged product containing one lyophilized active component packet and one buffer component packet shall be the earlier of the two expiration dates.

2. Background

Cholera is an acute enteric infection caused by the bacterium *Vibrio cholerae* O1 or O139 and is transmitted by the ingestion of water or food containing the organism. The illness principally occurs in countries with insufficient access to safe water and proper sanitation, with even more dramatic impact in areas where basic environmental infrastructures are disrupted or have been destroyed. Contaminated water supplies are the main source of cholera infection, although raw shellfish, uncooked fruits and vegetables and other foods also can harbor *V. cholerae* and therefore present a risk of infection. The infectious dose of wild type cholera infection in humans is in the range of $10^2 – 10^6$ bacteria. Cholera is characterized in its most severe form (cholera gravis) by a sudden onset of acute electrolyte-rich watery diarrhea that can lead to severe dehydration and death. The extremely short incubation period (approximately 12 hours to 5 days) contributes to the sometimes sudden onset of outbreaks and the quick rise in number of cases. Cholera remains an important public health concern primarily in developing countries.

V. cholerae is classified by serogroup (O1 or O139). The O1 serogroup consists of two biotypes, classical and El Tor, and each is further divided into two serotypes, Ogawa and Inaba. Worldwide, *V. cholerae* O1 El Tor is currently the predominant biotype. An estimated 1.4 - 4.3 million cases and 28,000 - 142,000 deaths occur each year around the world[1]. In 2013, a total of 129,064 cases of cholera were reported worldwide, with 47.3% of those originating from an outbreak in Haiti and the Dominican Republic that started in October 2010. A total of 56,329 cases were reported from Africa, and 11,579 cases were reported from the Asian continent[1]. Cholera serogroup O139 emerged in the Bay of Bengal in 1992 but has remained confined to Southeast Asia and has not emerged as a significant threat, with only 37 cases reported in 2013 from China.

The serious and often deadly effects of the disease are the result of the potent oligomeric cholera toxin (CT), which the bacteria produce in the small intestine. The B subunit of CT mediates binding of the toxin to cells lining of the intestine via the monosialosyl ganglioside GM-1 receptor. The toxin is internalized and is transported to the endoplasmic reticulum, after which the active A subunit is released and enters the host cell cytosol. The A subunit interferes with the normal flow of sodium and chloride, causing active secretion of excessive amounts of water into the intestinal lumen, leading to diarrhea and a rapid loss of body fluid and electrolytes.

An integrated approach is required to prevent cholera. In addition to the improvement of water quality and sanitation, the focused use of oral cholera vaccines can assist in cholera control. Currently there are two inactivated two-dose cholera vaccines (Dukoral® [Crucell; Leiden, the Netherlands] and Shanchol™ [Shantha Biotechnics; Hyderabad, India]) available outside the U.S. Neither of these products is licensed in the U.S. Killed whole cell cholera vaccines were previously licensed in the U.S.; however, these are no longer manufactured. Hence, at this moment there is no cholera vaccine available for U.S. travelers.

The attenuated recombinant *V. cholerae* O1 strain CVD 103-HgR was developed at the Center for Vaccine Development (CVD) at University of Maryland, Baltimore. The vaccine strain was constructed by deleting 94% of the domain encoding the A (ADP ribosylating) subunit of cholera toxin from the wild-type *V. cholerae* O1 classical Inaba strain 569B and inserting a gene encoding resistance to mercury into the hemolysin A (*hlyA*) locus, to inactivate hemolysin A toxin and to provide a marker to easily differentiate the vaccine strain from wild type *V. cholerae* O1. This resulted in *V. cholerae* O1 Inaba Vaccine Strain CVD 103-HgR, which is able to synthesize the immunogenic nontoxic B subunit of CT (encoded by the *ctxB* gene).

In 1987, vials of the original CVD 103-HgR progenitor strain were transferred from CVD to the Swiss Serum and Vaccine Institute (SSVI) and were used to produce the Master Seed Lot for Orochol (the commercial name used globally except in North America) or Mutacol Berna (the commercial product name in North America). In 1997, a Product License Application/Establishment License Application for Mutacol was filed in the U.S., but the licensing process was never completed. A large randomized, double-blind, placebo-controlled efficacy trial of one dose of CVD 103-HgR live oral cholera vaccine ($5x10^9$ CFU dose) was conducted in Jakarta, Indonesia in 67,508 persons 2 to 41 years of age between July 1993 and December 1997 to examine efficacy against endemic *V. cholerae* O1 El Tor. In this endemic population, this vaccine showed only 18% efficacy at one year follow-up, 2.3% over two years, and a cumulative 13.5% vaccine efficacy with a lower bound of the two-sided 95% CI of (-)24% over four years[2].

In 1993 and 1998, CBER convened Vaccines and Related Biologics Products Advisory Committee (VRBPAC) meetings to consider whether data from human cholera challenge studies in U.S. subjects could be sufficient to demonstrate the effectiveness of a cholera vaccine in travelers to endemic areas, who are at high risk for contracting the disease. In 1998, in light of the Indonesian field trial results, the Committee agreed that human challenge studies could suffice to demonstrate effectiveness of a cholera vaccine in persons not previously

exposed to cholera who plan to travel to cholera endemic areas, provided that studies were adequate and well-controlled and were conducted under the provisions of Good Clinical Practice (GCP).

The CVD 103-HgR vaccine strain was selected for redevelopment by PaxVax, since it was known to be effective in human cholera challenge studies conducted in the past in non-cholera-endemic countries[3,4] and hence could be suitable for use by persons from the U.S. who would be at risk of infection with cholera when visiting cholera-affected areas. The extensive clinical studies conducted in support of the Orochol development program provided evidence of a favorable benefit-risk profile of CVD 103-HgR in the non-endemic setting.

During the IND review process for this product, CBER conducted extensive discussions with PaxVax concerning design of clinical studies, appropriate serological endpoints, and clinical serology methodology.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Product Composition

VAXCHORA is supplied as a single-dose foil packet containing buffer (buffer component) and an accompanying single-dose foil packet of lyophilized CVD 103-HgR (active component). The other ingredients in the active component packet are sucrose, sodium chloride, ascorbic acid, dried lactose, and Hy-Case SF (hydrolyzed casein). The buffer component packet contains sodium bicarbonate, sodium carbonate, ascorbic acid and lactose. The composition of the VAXCHORA final drug product and the functions of the ingredients are provided in Table 1.

Table 1: Composition of VAXCHORA Final Drug Product

Ingredient	Function	Amount/Dose
Active component		
Viable CVD 103-HgR	Active ingredient	$4x10^8$ to $2x10^9$ CFU
Sucrose	Cryoprotectant	≤ 165.37 mg
Sodium Chloride	Stabilizer	≤ 17.11 mg
Hy-Case SF	Stabilizer (Cryoprotectant)	≤ 17.11 mg
Ascorbic acid	Stabilizer (Anitoxidant)	≤ 8.55 mg
Dried Lactose	Stabilizer (Desiccant) and Bulking Agent	≤ 2.09 g
Buffer component		
Sodium Bicarbonate	Buffer	2.16 – 2.41 g
Sodium Carbonate	Buffer	0.24 – 0.49 g
Ascorbic Acid	Buffer; Water Chlorine Neutralizer	1.5 – 1.8 g
Dried Lactose	Manufacturer Flowability	0.18 – 0.22 g

Presentation and Packaging System

VAXCHORA is supplied in a foil packet of lyophilized bacteria and is co-packaged with the buffer. To reconstitute the vaccine, the contents of the buffer component packet are dissolved in 100 mL of bottled purified water, followed by adding the contents of the active component packet and mixing the solution. The vaccine is taken orally.

Manufacturing Overview

VAXCHORA active component drug product (DP) consists of lyophilized dried powder of CVD 103-HgR drug substance blended with dried lactose. The intermediate bulk drug substance (IBDS) was produced at (b) (4) . Processing of the IBDS to vaccine drug substance, manufacture of the final formulated vaccine drug product, filling of the vaccine drug product, and labeling and primary packaging of the vaccine drug product were performed at PaxVax's (b) (4) , facility.

Drug Substances

The Drug Substance (DS) is PXVX0200, also known as CVD 103-HgR. The strain was genetically engineered from wild type *V. cholerae* O1 classical Inaba strain 569B. Starting from CVD 103-HgR Lot (b) (4) generated the master seed lot (MSL) and working seed lot (WSL). Beginning in January 2015, PaxVax used (b) (4) as a contract laboratory for production of WSL.

The IBDS is manufactured from the CVD 103-HgR WSL through (b) (4) . In-process tests for manufacture of the IBDS are: (b) (4) . Release testing of IBDS includes: (b) (4) IBDS was shipped to PaxVax's (b) (4) facility for further processing to BDS and DP, followed by filling. At PaxVax's (b) (4) facility, the IBDS is received and stored at (b) (4) . The (b) (4) containing the IBDS are (b) (4) . The IBDS is (b) (4) resulting in the BDS. The BDS is (b) (4) of BDS are stored at (b) (4) . Each lot of IBDS yields approximately (b) (4) of BDS.

To demonstrate reproducibility of the IBDS and BDS manufacturing processes, process validations were performed. Physicochemical properties of PXVX0200 and their characterization methods include: (b) (4)

(b) (4) . PXVX0200 specifications are presented in Table 2.

Parameters used to assess stability of the BDS include: (b) (4) At the long-term storage condition of (b) (4), all acceptance criteria were met for all batches through the time points for which data are available, supporting a proposed shelf life for the BDS of (b) (4) when stored at (b) (4)

Table 2: PXVX0200 Drug Substance Specifications

(b) (4)

(b) (4)

Drug Product (Active component)

The active portion of the vaccine is PXVX0200 (active component), which consists of a single-dose, multilayer foil packet containing lyophilized bacteria. In the same package, a separate single-dose packet contains buffer powder. The dose is $4x10^8$- to $2x10^9$ CFU of recombinant live attenuated *V. cholerae* strain CVD 103-HgR. Specifications for the active component DP are shown in Table 3.

Steps in active component DP manufacturing include IBDS receipt and storage, milling and mixing to form BDS, blending with dried lactose to form active component BDP, and filling and packaging to form active component DP.

Critical process parameters are (b) (4)

During packet filling, critical process parameters are: (b) (4)

Tests performed on active component DP on stability are appearance, viable cell count, moisture, and (b) (4) . Based on 18 months of real-time data for the clinical trial material (CTM) lots, PaxVax proposes a commercial shelf life of 18 months when the active component DP is stored at -20 ± 5°C.

Table 3: VAXCHORA Drug Product Specifications

Quality Attribute	Analytical Procedure	Acceptance Criteria
Description		
Appearance	PaxVax Q108[a]	White to beige powder, no visible foreign particles
Visual Control	PaxVax Q108	Off-white packet, two visible black (registration) marks on each side of the packet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the packet on all 4 sides and lot number and date of manufacture expiry printed on the packets is accurate and legible
Identity		
(b) (4) Assay	(b) (4)	(b) (4)
General		
Moisture Content	PaxVax Q193 a (b) (4)	(b) (4)
Packet Integrity Test	PaxVax Q211	Inspection Level II with AQL of (b) (4) Failures have defect of (b) (4)
Potency		
Viable cell count	PaxVax Q217[a]	$4x10^8$ to $2x10^9$ CFU/dose
Safety		
(b) (4)	(b) (4)	(b) (4)
Absence of Specific Organisms: (b) (4)	(b) (4)	(b) (4)

[a] Methods used for release and stability

Drug Product (Buffer)

The functions of the buffer are to provide the (b) (4) for the active component DP during reconstitution and to stabilize the active component DP after oral administration by neutralizing stomach acid.

The manufacturing process includes the following steps: (b) (4) final blending; packaging, storage, and shipping of buffer BDP to PaxVax; and receipt, storage, and filling of buffer into packets. Buffer final DP is stored at (b) (4) prior to shipment to a secondary packager, where each packet is placed into a carton along with a active component DP packet. Long-term storage is at -20°C. The critical

quality attributes are appearance, ascorbic acid content, (b) (4), (b) (4) and microbiological tests. The release specification includes review of the tests listed on the certificate of analysis, appearance, identity of carbonates and bicarbonates, and identity of lactose.

Stability tests for the buffer component DP conformance lots are appearance, reconstitution time, (b) (4), ascorbic acid assay, (b) (4), and (b) (4). Based on the long-term stability results for three conformance lots and the results for the pilot lot stored at the long-term and accelerated conditions, PaxVax proposes a shelf life for the buffer component DP of 24 months at -20°C, which is acceptable.

Packaging and Testing of DP:

Manufacturing and primary packaging of the active component DP was conducted at PaxVax's (b) (4), facility. Manufacturing of the buffer BDP is performed by (b) (4) Secondary packaging of both the active component DP and buffer component DP is performed by (b) (4) Commercial testing is conducted by three companies: PaxVax [release and stability testing (except identity by (b) (4); release testing- identity by (b) (4) and (b) (4); release and stability testing- (b) (4); release testing- (b) (4)

Extractables and Leachables (E/L):

(b) (4) are used during manufacturing of IBDS at the (b) (4) facility, which are made of (b) (4), materials that present little risk of leachables or extractables. PaxVax provided test results for leachables and extractables for (b) (4) which was found acceptable.

GST exemption:

In the original submission, PaxVax included the General Safety Test (GST) as a release test. As this test is no longer required for biological products, based on CBER's recommendation, PaxVax removed the GST from the active component and buffer component specifications.

Container Closure System:

The drug product is filled into 60 mm x 90 mm packets made from three-ply, multi-layer foil (b) (4) The packets are heat-sealed on all four sides with a minimum width of (b) (4) from the inner weld line to the outer edge. PaxVax conducted container closure integrity testing on the foil packets in-house using a non-destructive, (b) (4) method; all acceptance criteria were met.

CMC Review Issues:

A major CMC issue that arose and was resolved during the BLA review related to the source of WSL. The clinical studies described in the BLA were conducted with active component DP that was manufactured using the (b) (4) WSL. Beginning in January 2015, PaxVax used (b) (4) to manufacture WSL. However, the data that were provided in support of (b) (4) as a contract manufacturer of WSL were insufficient. BLA approval is for final DP manufactured using WSL made by (b) (4) CBER requested more detailed information regarding the (b) (4) facilities, including cleaning verification and validation of all the equipment used to manufacture WSL, as well as all manufacturing information and testing data from three lots of final DP manufactured using (b) (4) WSL. At CBER's recommendation, PaxVax agreed to submit a Prior Approval Supplement (PAS) for use of (b) (4) as the WSL manufacturer post approval of this licensing application.

Other minor CMC-related issues that came up during the review process and were resolved included: transfer and storage conditions (b) (4) and procedures of MSL and WSL, length of BDS hold at (b) (4), results for leachables and extractables, stability studies details, SOPs for (b) (4) and viable cell count, plate counts used for validation of determination of plate count, inclusion of moisture content in the release testing for the buffer component DP, including an alert limit to the bioburden specification for the DP (b) (4), qualification of (b) (4) detection under Microbial Limit Testing (b) (4) for (b) (4) the DP (b) (4), and the type of bottled water used to reconstitute the vaccine and its impact on vaccine potency.

b) CBER Lot Release

The lot release protocol templates were submitted to CBER for review and found to be acceptable after revisions. Samples from three lots of VAXCHORA were submitted in support of the BLA for lot release testing and were found to be acceptable. For routine lot release, PaxVax will submit final container samples along with lot release protocols showing all applicable tests. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of VAXCHORA are listed in the table below. The activities performed and inspectional histories are noted in Table 4 and are further described in the paragraphs that follow.

Table 4: Manufacturing Facilities for VAXCHORA (Cholera Vaccine Live, Oral)

Name/Address	FEI number	DUNS number	Inspection/ waiver	Result/ Justification
(b) (4) *Intermediate Bulk Drug Substance* Manufacturing	(b) (4)	(b) (4)	Pre-License (PLI) Inspection	CBER (b) (4) VAI
PaxVax, Inc. (b) (4) *Bulk Drug Substance,* and *Drug Product*, Manufacturing (formulation, fill/finish) and labeling	(b) (4)	(b) (4)	PLI	CBER (b) (4) NAI
(b) (4) *Drug Product* Testing	(b) (4)	(b) (4)	Inspection Waived	ORA (b) (4) NAI
(b) (4) *Drug Product* Testing	(b) (4)	(b) (4)	Inspection Waived	ORA (b) (4) NAI

CBER performed a PLI of (b) (4) from (b) (4), covering the manufacture of intermediate bulk drug substance. At the end of the inspection, CBER issued a Form FDA 483 with two observations. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

CBER performed a PLI of PaxVax, Inc. from (b) (4), covering drug product manufacturing, filling and labeling. No issues were identified and no Form FDA 483 was issued.

ORA conducted a surveillance inspection of (b) (4). from (b) (4). The inspection was classified as NAI. No issues were identified.

ORA conducted a surveillance inspection of (b) (4) from (b) (4) The inspection was classified as NAI. No issues were identified.

d) Environmental Assessment

PaxVax has submitted an environmental assessment (EA) in accordance with 21 CFR 25 and addressed the risk of shedding of the vaccine strain by vaccinees (for details please see section 7b: Shedding and Transmission of VAXCHORA). The vaccine strain would not be expected to survive sewage treatment processes. The applicant has addressed the risk of reversion of the vaccine strain to toxicity. No significant environmental impacts were identified, and a finding of no significant impact was issued. The potential environmental exposure and environmental stability of the vaccine are expected to be minimal. During manufacturing of bulk drug substance of VAXCORA at the (b) (4) facility, all liquid waste is treated by heat or chemicals to inactivate all biohazards. Therefore, the risk of contamination of the environment during manufacture of the vaccine is negligible.

4. Nonclinical Pharmacology/Toxicology

As *V. cholerae* is a strictly human pathogen[5], there is no valid animal model available to assess non-clinical safety of this vaccine or predict the mucosal immune response to this live attenuated cholera vaccine. Therefore, nonclinical animal safety or toxicology studies were not included in the BLA. This plan was discussed with CBER during the pre-IND correspondence, and CBER agreed with PaxVax's proposal. The VAXCHORA clinical trial safety data described in this application and the extensive previous human experience with the CVD 103-HgR strain demonstrate a favorable safety profile in clinical use.

5. Clinical Pharmacology

Mechanism of Action

Cholera infection provides prolonged protective immunity against subsequent infection [6-8]. This immunity is mediated by local mucosal secretory IgA (SIgA) antibodies produced in the small intestine and directed primarily against lipopolysaccharide (LPS) and the cholera toxin B subunit (CTB). Immunological memory (antigen-specific B cells) is also induced. The anti-LPS SIgA antibodies prevent the establishment of bacterial colonization; the anti-CTB SIgA antibodies neutralize the cholera holotoxin and prevent it from binding to the cells of the small intestine[9]. An immune marker associated with this mucosal immune response is the presence of vibriocidal antibodies in the serum (SVA). Furthermore, it has been shown that the presence of SVA in subjects previously exposed to cholera is associated with protection against subsequent infection[10]. The CVD 103-HgR vaccine strain was designed to induce a similar immune response to natural cholera infection without causing cholera disease. The strain is attenuated via a 94% deletion of the domain encoding the active A subunit of cholera toxin, hence preventing the formation of toxin-associated symptoms such as diarrhea.

VAXCHORA has been shown to induce SVA, serum anti-CT antibodies, peripheral blood anti-LPS, anti-CT IgG memory B cells and to be protective against cholera challenge. Because it is a live attenuated strain, administered orally, it would also be expected to induce a local mucosal immune response in the small intestine in a similar way to wild type *V. cholera*e infection. The presence of anti- LPS SIgA antibodies in stool samples from vaccine recipients receiving the CVD 103-HgR strain has been demonstrated in an earlier study[11] and was therefore not studied in any of the VAXCHORA trials.

6. Clinical/Statistical

a) Clinical Program

Cholera is a serious condition for U.S. residents traveling to cholera affected areas because: 1) residents typically do not have immunity to cholera, 2) strategies to contain and control cholera are not fully implemented in many underdeveloped regions creating opportunities for cholera exposure, 3) the CDC and World Health Organization (WHO) recommended prevention practices cannot always be consistently adhered to, and 4) a U.S. licensed cholera vaccine is not available.

Currently there are two inactivated two-dose inactivated cholera vaccines (Dukoral® [Crucell; Leiden, the Netherlands] and Shanchol™ [Shantha Biotechnics; Hyderabad, India]) available outside the U.S. Neither of these products is licensed in the U.S. Killed whole cell cholera vaccines were previously licensed in the U.S.; however, these are no longer manufactured. Hence, at this moment there is no cholera vaccine available for U.S. travelers.

The CVD 103-HgR vaccine strain was selected for redevelopment by PaxVax since it was known to be effective in human cholera challenge studies conducted in the past in non-cholera endemic countries[2,3] and hence was deemed suitable for use by persons from the U.S. without previous exposure to cholera who would be at risk of infection when visiting cholera affected areas. The extensive clinical studies conducted in support of the Orochol development program provided evidence of a favorable benefit-risk profile of CVD 103-HgR in individuals not previously exposed to cholera and thus, supported the PaxVax's redevelopment plan.

General Description of Clinical Studies

PaxVax submitted data from four clinical studies as part of this BLA (Table 5). Two Phase 3 clinical studies supported vaccine effectiveness(PXVX-VC-200-003 and PXVX-VC-200-005), one Phase 3 clinical study demonstrated manufacturing consistency (PXVX-VC-200-004), and one Phase 1 study provided shedding and transmission data (PXVX-VC-200-002). Each of the four clinical studies contributed to the safety database. In lieu of a field efficacy trial in an endemic area, PaxVax conducted a human challenge study (PXVX-VC-200-003) to evaluate the effectiveness of a single dose of VAXCHORA against moderate to severe diarrhea in 18 through 45 year old adults, with no history of natural cholera infection or experimental challenge with cholera. VAXCHORA will be the first vaccine licensed in the U.S. for which effectiveness has been demonstrated based on human challenge data.

Table 5: Clinical Studies of Safety and Immunogenicity in Participants 18 through 64 Years of Age

Type of Trial	**Trial No.**	**Objective of the Trial**	**Dose of vaccine** CFU/dose, Oral	**Number of subjects (vaccine, placebo)**	**Age**
Phase-1	PXVX-VC-200-002 NCT01585181	Safety,immunogenicity and shedding	4.34×10^8	66 (55 vaccine, 11 placebo)	18-50
Phase-3	PXVX-VC-200-003 NCT01895855	Demonstrate protection from live cholera challenge	5×10^8	197 (95 vaccine, 102 placebo)	18-45
Phase-3	PXVX-VC-200-004 NCT02064586	Demonstrate clinical lot consistency	1×10^9	3146 (2795 vaccine, 351 placebo)	18-45
Phase-3	PXVX-VC-200-005 NCT02100631	Demonstrate equivalence in immune response of older and younger adults	1×10^9	398 (299 vaccine, 99 placebo)	46-64

Vaccine Effectiveness

Evaluating the effectiveness of vaccines for prevention of cholera disease is challenging. The use of a human challenge trial to demonstrate effectiveness has been accepted by CBER as a basis for licensure of a cholera vaccine for travelers, because the low incidence of cholera in travelers has made field trials impractical to support an indication for use of this vaccine in US travelers. At the May 27, 1998 VRBPAC meeting, the committee agreed that human challenge studies could be an adequate source of effectiveness data for a vaccine indicated for travelers visiting countries in which cholera is not endemic.

Study PXVX-VC-200-003 was a randomized, double-blind, placebo-controlled *V. cholerae* challenge study conducted in the U.S. Subjects 18 through 45 years of age (N=197) with no prior history of cholera infection or travel to a cholera-endemic area in the previous 5 years, Subjects were randomized according to a 1:1 ratio to receive one dose of $5x10^8$ CFU of VAXCHORA or placebo. The subset of subjects to be challenged (N=134) was selected from the pool of all subjects using a random procedure stratified to ensure roughly equal balance between vaccine and placebo recipients so that at least 60% of subjects in each challenge group had blood type O. Individuals with type O blood are less likely to be infected, but if infected, they are at increased risk for developing severe cholera.

Of the 95 VAXCHORA recipients, 68 were challenged; 35 were challenged at 10 days post-vaccination and 33 were challenged at 3 months post-vaccination. Of the 102 placebo recipients, 66 were challenged; 33 were challenged at 10 days post-vaccination and 33 at 3 months post-vaccination. Overall, the mean age of the challenge population was 31.4 years. More males were challenged in the vaccine group (76.5%) compared to the placebo group (57.6%). Overall by race, 70.9% of the challenge population was Black, 25.4% were White, 0.7% were American Indian/Alaskan Native, 0.7% were Asian, and 2.2% were other. By ethnicity, there were 3.7% Hispanic or Latino participants. Overall, 56.0% of challenged subjects had blood type O.

The heterologous challenge consisted of administration of $1x10^5$ CFU live wild type *V. cholerae* El Tor Inaba N16961 at 10 days or 3 months post-vaccination. The co-primary objectives were to demonstrate the effectiveness of a single dose of VAXCHORA in the prevention of moderate to severe diarrhea following challenge at 10 days and 3 months post-vaccination. Moderate to severe diarrhea was defined as cumulative diarrheal purge ≥ 3 liters (L) within 10 days after challenge. Vaccine effectiveness at 10 days post-vaccination was 90.3% (95% CI; 62.7% - 100.0%). At 3 months post-vaccination, vaccine effectiveness was 79.5% (95% CI; 49.9% - 100.0%) (Table 6).

Table 6: Vaccine Effectiveness in the Prevention of Moderate to Severe Diarrhea Following Heterologous Challenge at 10 Days and 3 Months Post-Vaccination (Intent-to-Treat Population) Study PXVX-VC-200-003

Parameter	**VAXCHORA 10 Day Challenge** N=35 n (%)	**VAXCHORA 3 Month Challenge** N=33 n (%)	**Combined Placebo[a] 10 Day or 3 Month Challenge** N=66 n (%)
Moderate or Severe Diarrhea (≥ 3.0 L)[b]	2 (5.7%)	4 (12.1%)	39 (59.1%)
Vaccine Effectiveness [c]	90.3% (95% CI; 62.7% - 100.0%)	79.5% (95% CI; 49.9% - 100.0%)	

[a] Combined placebo group comprised of all placebo recipients who were challenged at either 10 days (N=33) or 3 months (N=33) following vaccination.

[b] Attack Rate: Moderate (≥ 3L to 5L of diarrhea) or severe diarrhea (> 5 L of diarrhea) within 10 days after challenge

[c] Vaccine Effectiveness = [(Attack Rate in Placebo Group – Attack Rate in Vaccine Group)/Attack Rate in Placebo Group] x 100.

Clinical Immunogenicity Data

Direct evidence of protection against cholera disease was derived from a Phase 3 placebo-controlled human challenge study (PXVX-VC-200-003) in volunteers 18 - 45 years old. Protection was assessed by challenging volunteers 10 days or 3 months post-vaccination. Data from this trial indicated that serum vibriocidal antibody titers against *V. cholerae* O1 classical Inaba measured at 10 days post-vaccination were associated with protection. CBER and PaxVax agreed that seroconversion (defined as a ≥ 4-fold increase over baseline titer) of classical Inaba serum vibriocidal antibody at 10 days post-vaccination could be used as an immunologic parameter for bridging effectiveness from 18 through 45 year olds to 46 through 64 year olds.

Exploratory analyses were performed to determine the relationship between vibriocidal and/or anti-CT antibody titers and the incidence of moderate/severe cholera in the 10 days or 3 months post-vaccination cohorts in the challenge study. Analysis revealed that seroconversion at 10 days post-vaccination in vibriocidal antibody titer had a significant association with

protection against moderate/severe cholera in both the 10 days or 3 months post-vaccination challenge studies. The rates of seroconversion were 94% for the 10 days post-vaccination challenge group and 88% for the 3 months post-vaccination challenge group. In contrast, the seroconversion rates for the placebo group (challenged) was only 2%.

Study PXVX-VC-200-004 was a randomized (8:1), double-blind, placebo-controlled lot consistency and safety study in 18 through 45 year olds. A total of 3,146 subjects were enrolled and randomized to lot A (927 subjects), lot B (933 subjects), lot C (935 subjects), and placebo group (351 subjects). The primary objective of the PXVX-VC-200-004 study (lot consistency) was to demonstrate immunologic equivalence of three different production lots (A, B and C) of VAXCHORA when (a) primary endpoint was serum vibriocidal antibody measured at 10 days post-vaccination, and (b) the equivalence criterion was that the 95% confidence interval (CI) around each pairwise ratio of GMTs be within (0.67, 1.5). The 95% CI around each pairwise ratio of geometric mean titers was (0.78, 1.08) comparing Lots A:B, (0.87, 1.20) comparing Lots B:C, and (0.80, 1.10) comparing Lots A:C respectively. A secondary objective of the lot consistency study was to estimate the seroconversion rate by vibriocidal antibody 10 days post-vaccination. Seroconversion was 94% (95% CI; 93% - 94%) in vaccine recipients and 4% (95% CI;2% - 7%) in placebo recipients by 10 days post-vaccination. The seroconversion rates among VAXCHORA recipients in this study served as a historical control comparator group in the bridging analyses in study PXVX-VC-200-005.

Study PXVX-VC-200-005 was a randomized (3:1), double-blind, placebo-controlled immunogenicity study in 46 through 64 year old adults. The effectiveness of VAXCHORA in 46 through 64 year old adults was based on a non-inferiority comparison of the vaccine-induced immune response in subjects 18 - 45 years of age enrolled in Study PXVX-VC-200-004 and subjects enrolled in PXVX-VC-200-005. This bridging was accomplished using the same vaccine dose and lot, and Day 11 post-vaccination SVA evaluated by the same validated assay for both studies. For the bridging, PXVX-VC-200-004 was used rather than the challenge study to allow for improved statistical power for the non-inferiority comparison and to set a more rigorous standard for demonstration of non inferiority. Furthermore, study PXVX-VC-200-004 used a higher dose of VAXCHORA than was used in the challenge study (refer to Table 5). Important in determining the bridging strategy was the evidence provided in the BLA supporting the association between Day 11 SVA seroconversion rate and protection against moderate/severe diarrhea in the challenge study PXVX-VC-200-003.

The primary objective of PXVX-VC-200-005 was to demonstrate that seroconversion by classical Inaba vibriocidal antibody at 10 days post-vaccination in older adults ages 46 - 64 years was non-inferior to seroconversion at 10 days post-vaccination in younger adults ages 18-45 years following vaccination with VAXCHORA. Seroconversion was defined as a $\geq$4-fold rise above baseline titer. The non-inferiority criterion was that the lower bound of the two-sided 95% CI on the difference in seroconversion between older and younger adults be greater than -10 percentage points. To demonstrate an acceptable immunogenicity of the vaccine among the older adults, the lower bound of the two-sided 95% CI on seroconversion by classical Inaba vibriocidal antibody at 10 days post-vaccination needed to be greater than 70% in older adults ages 46 - 64 years following vaccination with VAXCHORA. The younger

adult comparator group used for bridging analyses consisted of the Immunogenicity Evaluable Population from the lot consistency study.

Seroconversion of 90.4% (95% CI; 86.4% - 93.5%) of older subjects and 93.5% (95% CI; 92.5% - 94.4%) of younger subjects by classical Inaba vibriocidal antibody was reported, and the lower bound of the two-sided 95% CI on the difference in seroconversion rates between older and younger adults was −6.7%. The lower bound of the two-sided 95% CI on seroconversion in older adults was 86.4% (Table 7).

Table 7: Vibriocidal Antibody Seroconversion Against Classical Inaba *V. cholerae* Vaccine Strain at 10 Days Post-Vaccination in PXVX-VC-200-005 Compared to PXVX-VC-200-004 [Bridging Analysis Population]

Study	**VAXCHORA** N Analyzable [a]	**VAXCHORA Seroconversion 10 Day post vaccination** % [95% CI]	**Placebo** N Analyzable [a]	**Placebo Seroconversion 10 Day post vaccination** % [95% CI]
PXVX-VC-200-004 (18 through 45 year olds)	2687	93.5% [92.5%, 94.4%]	334	4.2% [2.3%, 6.9%]
PXVX-VC-200-005 (46 through 64 year olds)	291	90.4% [86.4%, 93.5%]	99	0.0% [0.0%, 3.7%]

[a] N Analyzable was the number of subjects with analyzable samples at both Day 1 and Day 10 post-vaccination.

V. cholerae serogroup O1 consists of four major subtypes: classical Inaba, classical Ogawa, El Tor Inaba and El Tor Ogawa. Serum vibriocidal antibody against the three types of *V. cholerae* not contained in the vaccine, namely classical Ogawa, El Tor Inaba and El Tor Ogawa, was also measured in PXVX-VC-200-004 and PXVX-VC-200-005. The percentages of vaccine recipients who seroconverted against each of the 4 major biotype/serotypes of *V. cholerae* serogroup O1 at 10 days post-vaccination (71.4% to 91.0%) are shown in Table 8.

Table 8: Seroconversion Rates[a] 10 Days Post-Vaccination for the Four Major *V. Cholerae* O1 Serogroup Biotypes and Serotypes in Studies PXVX-VC-200-003 and PXVX-VC-200-005 (Immunogenicity Evaluable Population)

Cholera Strain	PXVX-VC-200-003) (18 through 45 year olds) VAXCHORA N=93 % (95% CI])	PXVX-VC-200-005) (46 through 64 year olds) VAXCHORA N=291 % (95% CI)	Total Placebo N=201 % (95% CI)
Classical Inaba	90.3% [82.4%, 95.5%]	90.4% [86.4%, 93.5%]	2.9% [1.7%, 4.7%]
El Tor Inaba	91.4% [83.8%, 96.2%]	91.0% [87.1%, 94.1%]	4.5% [2.1%, 8.5%]
Classical Ogawa	87.1% [78.5%, 93.2%]	73.2% [67.7%, 78.2%]	2.5% [0.8%, 5.8%]
El Tor Ogawa	89.2% [81.1%, 94.7%]	71.4% [65.8%, 76.5%]	5.6% [2.8%, 9.7%]

[a] Percentages of subjects who had at least a 4-fold rise in vibriocidal antibody titer over the titer measured at Day 1.

Bioresearch Monitoring

The CBER Bioresearch Monitoring (BIMO) Branch issued four clinical investigators inspections for three pivotal Phase 3 clinical studies in support of this BLA. The four clinical sites were selected based on subject enrollment for each protocol, previous inspectional history, and geographic location. Information submitted in the BLA was compared to source documents at these sites. The BIMO inspection of four clinical investigators did not reveal substantive problems that impact the data submitted in the application.

INSPECTION SITES:

Bioresearch Monitoring inspections were conducted at the following clinical sites:

Site Number	Location	Protocols	Form FDA 483 Issued	Final Classification
03	Cincinnati, OH	PXVX-VC-200-003	No	NAI
04	Burlington, VT	PXVX-VC-200-003	Yes	VAI
04	Burlington, VT	PXVX-VC-200-005	No	NAI
13	Lenexa, KS	PXVX-VC-200-004 PXVX-VC-200-005	No	NAI
15	Salt Lake City, UT	PXVX-VC-200-004 PXVX-VC-200-005	Yes	VAI

NAI = No Action Indicated, VAI = Voluntary Action Indicated

b) Pediatrics

Under the Pediatric Research Equity Act (PREA), the requirement for studies in children ages 0 to less than 2 years was waived because in this age group VAXCHORA is not likely to be

used in a substantial number of pediatric patients and does not represent a meaningful therapeutic benefit over existing measures recommended by the Centers for Disease Control (CDC) for the prevention of cholera. Children younger than 2 years of age traveling to cholera affected areas whose parents follow CDC's recommendations for the prevention of cholera, would have little chance of exposure to contaminated food or water. Breastfeeding and/or feeding formula prepared with sterile water would further reduce the possibility of exposure to contaminated food or water. Furthermore, the low incidence of cholera among US children suggests that Vaxchora is not likely to be used by a substantial number of children less than 2 years of age.

Studies in children ages ≥ 2 years to <18 years were deferred because the product was ready for regulatory approval for use in adults and the pediatric study has not been completed. FDA's Pediatric Review Committee (PeRC) concurred with this decision on May 11, 2016.

7. Safety

a) Safety of VAXCHORA

A total of 3235 subjects were exposed to one oral dose of VAXCHORA (Table 5). In the Phase 1 safety and immunogenicity trial PXVX-VC-200-002, 55 subjects were exposed to a single dose of VAXCHORA containing $4.43x10^8$ CFU. In the Phase 3 live cholera challenge trial PXVX-VC-200-003, 95 subjects were exposed to a single dose of VAXCHORA containing $5x10^8$ CFU. In the Phase 3 lot consistency PXVX-VC-200-004 study and the study conducted in older adults, PXVX-VC-200-005, 2789 and 296 subjects, respectively, were exposed to a single dose of VAXCHORA containing $1x10^9$ CFU.

Vaccine and placebo recipients were well-matched by age, sex, ethnicity and blood type. The vaccine and placebo groups also had similar racial distributions within each individual trial in the program, but the percentage of black or African Americans in the vaccine group was lower than the percentage in the placebo group (25.7% vs. 36.3%, respectively), when data from all trials were combined. This imbalance arose mostly because the challenge trial contributed proportionally more subjects to the overall placebo group,18.1% of the total, than to the vaccine group where challenge subjects comprised only 2.9% of the total. Since the challenge trial had the highest proportion of black or African American subjects of any trial in the program, and it played a bigger role in the makeup of the overall placebo group, the placebo group ended up with a higher proportion of black or African Americans than the vaccine group. Overall, the mean age was 32.5 years with a median age of 30.0 years. Females comprised 53.8% of the population, and 52.6% of the population had non-O blood type. The race distribution was as follows: 67.1% white, 27.3% black or African American, 0.3% Native Hawaiian or Pacific Islander, 1.8% Asian, 1.7% multiracial, 1.3% other and 0.6% American Indian or Alaskan Native. Most subjects, 90.6%, were not Hispanic or Latino.

Soliciated adverse reactions after study product administration were reported 4% more frequently by vaccine recipients 50.08% [95% CI; 48.32% - 51.83%] than by placebo recipients 45.75% [95% CI; 41.54% - 50.01%]. In both the vaccine and placebo groups, most

reactogenicity (i.e., a specific set of systemic signs and symptoms solicited through Day 7 post-vaccination, as displayed in Table 9) was mild (grade 1), occurred within 1 to 3 days of vaccination, and had resolved within 3 to 5 days following vaccination. The most common signs and symptoms for both vaccine and placebo recipients were tiredness and headache. As expected a statistically significant difference between treatment groups was found for diarrhea. Diarrhea (defined as ≥4 loose stools per 24 hours) was reported in 115/3177 = 3.62% [3.00%, 4.33%] of vaccine recipients and 9/553 = 1.63% [0.75%, 3.07%] of placebo recipients.

Overall, for the one Phase 1 (through Day 181) and three Phase 3 trials (through Day 29), AEs were reported by 23.7% of vaccine recipients and 27.4% of placebo recipients, which were mostly mild in severity. The three most common AEs, in both vaccine and placebo groups, with an incidence in the range of 2% (range of 2.1% to 3.2%), were headache, fatigue, and upper respiratory tract infection. No meaningful differences were observed between vaccine and placebo recipients in the incidence of AEs by preferred term (PT) or grouped by system organ class (SOC). Differences in the incidence of AEs were not assessed for statistical significance.

Serious adverse events were uncommon, reported in 0.6% of vaccine recipients and 0.5% of placebo recipients, and none were considered related to study product.

Table 9 presents the frequency of solicited adverse reactions, which were recorded daily for 7 days after vaccination. Only diarrhea occurred in a higher proportion of vaccine recipients than placebo recipients (3.62% vs 1.63%).

Table 9: Summary of Reactogenicity Days 1-8 Safety Population in VAXCHORA Trial Participants 18 to 64 Years of Age

Reactogenicity 1-7 days Post Vaccination	**VAXCHORA** (N=3177)[a] %	**Placebo (Saline)** (N=553)[a] %
Tiredness	30.0	29.5
Headache	27.8	26.0
Abdominal Pain	18.3	17.0
Nausea/Vomiting	17.4	15.6
Diarrhea	3.6	1.6

[a] N represents number of subjects who completed a memory aid.

The most common adverse events from Days 1-29 post-vaccination which were considered related to treatment are presented in Table-10. There were no significant differences observed between the vaccine and placebo recipient groups.

Table 10: Summary of Most Common Related Adverse Events – Safety Population

Related Adverse Events Day 1 through Day 29 Post-Vaccination[a,b]	VAXCHORA (N=3235) %	Placebo (N=562) %
Fatigue	1.2	2.5
Flatulence	0.9	0.9
Headache	0.9	1.1
Abdominal Pain	0.6	0.5
Decreased Appetite	0.6	0.9

Note: The adverse events in this table are those observed at a frequency of ≥0.5% in recipients of VAXCHORA.
Note: Percentages are based on the number of subjects in PXVX-VC-200-002 (Phase 1), PXVX-VC-200-003 (Challenge), PXVX-VC-200-004 (Lot), and PXVX-VC-200-005 (Older). The denominator represents the total number of subjects who received treatment combined across all trials. Only treatment-emergent adverse events are presented. Challenge-emergent adverse events are excluded.
Note: "Related" means events considered at least possibly related to treatment by the investigator.
a: Adverse events were collected through Day 181 for the 66 subjects in Phase I trial PXVX-VC-200-002.
b: All adverse event terms were coded using MedDRA dictionary version 15.0.

Overall, of the 3797 participants in the clinical studies, 20 (0.6%) vaccine recipients reported an SAE compared with 3 (0.5%) of placebo recipients. None of the SAEs were judged to be related to vaccine by the study investigator. One death due to suicide in a 38 year old occurred 84 days after receipt of VAXCHORA; this death was not considered to be caused by vaccination.

b) Shedding and Transmission of VAXCHORA

The randomized, double-blind, placebo-controlled Phase 1 trial enrolled 66 volunteers (55 vaccine recipients and 11 placebo recipients) and also 28 of their household contacts (HHCs) (24 HHC of vaccine recipients and 4 HHC of placebo recipients) for the purposes of evaluating the extent of vaccine bacteria shedding by vaccine recipients and potential for transmission of the vaccine bacteria from vaccine recipients to their contacts. Potential transmission of the vaccine organism from vaccine recipients to their HHCs was monitored via detection of either shedding and/or serum vibriocidal antibodies in HHCs. Shedding of *V. cholerae* O1 following vaccination was monitored via the collection and culture of stool samples or rectal swabs. Data were available from approximately half of vaccine recipients at Days 1, 3, and 7 post-vaccination and from the remainder of the vaccine recipients at Days 2, 4, and 7 post-vaccination. Shedding of vaccine occurred in a total of 11.3 % (95% CI, 4.3% - 23%) of vaccine recipients. Shedding increased in frequency over the week following vaccination, reaching a peak at Day 7 when it was detected in 7.3% (95% CI, 2.0 - 17.6) of vaccine recipients (Table 11). Vibriocidal antibodies were measured from HHCs using serum samples collected at baseline and day 28. No HHCs were seroconverted. No appreciable rise in vibriocidal antibody was detected in any HHC. There was no microbiological evidence of transmission of the vaccine organism from vaccine recipient to HHC. *V. cholera* O1 Inaba was not detected in either stool samples or rectal swabs collected 7 days post-vaccination for any of the 24 HHCs of vaccine recipients. One of 55 vaccine recipients (1.8%) experienced diarrhea in this trial, using the definition of the passage of 4 or more loose stools within 24 hours as a definition of diarrhea. A different definition of diarrhea (greater than 2 loose stools

per 24 hours) was stipulated in the Phase 1 trial, and using this definition, diarrhea was reported in 8 (14.5%) of vaccine and none of the placebo recipients.

The SVA seroconversion rate by 10 Day post vaccination was 83.3% (95% CI, 70.7% - 92.1%) and by Day 15 was 88.9% (95% CI, 77.4% - 95.8%) in vaccine recipients and zero in placebo recipients.

Table 11: Vaccinees with a Positive *V. cholerae* O1 Inaba Rectal Swab or Stool Sample (Vaccinee Safety Cohort (VAXCHORA Recipients Only) PXVX-VC-200-002

	VAXCHORA Number Positive/Number Assessed (%, 95% CI)	**VAXCHORA Number Positive/Number Assessed (%, 95% CI)**	**VAXCHORA Number Positive/Number Assessed (%, 95% CI)**
	Subgroup 1 (N=24)	**Subgroup 2 (N=31)**	**All Vaccinees (N=55)**
By Visit			
Days 1-2 Post Vaccination	0/24 (0.0%, 0.0%-14.2%)	1/31 (3.2%, 0.1%-16.7%)	1/55 (1.8%, 0.0%-9.7%)
Days 3-4 Post Vaccination	1/24 (4.2%, 0.1%-21.1%)	1/31 (3.2%, 0.1%-16.7%)	2/55 (3.6%, 0.4%-12.5%)
Day 7 Post Vaccination	3/24 (12.5%, 2.7%-32.4%)	1/31 (3.2%, 0.1%-16.7%)	4/55 (7.3%, 2.0%-17.6%)
Cumulative			
Through Day 2 Post Vaccination	0/24 (0.0%, 0.0%-14.2%)	1/30 (3.3%, 0.1%-17.2%)	1/54 (1.9%, 0.0%-9.9%)
Through Day 4 Post Vaccination	1/24 (4.2%, 0.1%-21.1%)	2/30 (6.7%, 0.8%-22.1%)	3/54 (5.6%, 1.2%-15.4%)
Through Day 7 Post Vaccination	4/24 (16.7%, 4.7%-37.4%)	2/30 (6.7%, 0.8%-22.1%)	6/54 (11.1%, 4.2%-22.6%)

Clinical Serology Assays

PaxVax submitted immunogenicity data based on serum vibriocidal antibody (SVA) titers, serum anti-toxin antibody titers (b) (4) , memory B cell responses (b) (4) against cholera toxin B subunit and cholera lipopolysaccharide (LPS). The performance of the cholera serum vibriocidal antibody titer assay and cholera toxin IgG (b) (4) quantitative assay were supported by validation and stability reports that were submitted to the BLA and were found to be adequate.

Subgroup Demographic Analyses

The observed rates of adverse events across different demographic groups based on race, gender, and age were fairly comparable and consistent with overall safety findings (for details, please see section 7b).

Concomitant vaccination or Medications

There are no data available to establish the safety and immunogenicity of concomitant administration of VAXCHORA with other vaccines. Concomitant administration of VAXCHORA with systemic antibiotics should be avoided since these agents may be active against the vaccine strain and prevent a sufficient degree of multiplication to occur in order to induce a protective immune response. Data from a study with a similar product indicate that the immune responses to VAXCHORA may be diminished when VAXCHORA is administered concomitantly with chloroquine. VAXCHORA should be administered at least 10 days before beginning antimalarial prophylaxis with chloroquine.

8. Advisory Committee Meeting

An advisory committee meeting was not convened during the review of this original BLA. Whether data from human cholera challenge studies in U.S. subjects could be sufficient to demonstrate the effectiveness of a cholera vaccine in U.S. travelers to endemic areas, who are at high risk for contracting the disease, was discussed during 1993 and 1998 VRBPAC meetings. In 1993, the Committee discussed the limitations of using data from clinical field trials of the CVD-103 HgR vaccine in endemic areas to predict the effectiveness of this vaccine in naïve U.S. travelers. During the 1998 VRBPAC meeting, failure of the CVD-103 HgR vaccine to show protection in the field trials was discussed, and the Committee agreed that human challenge studies could suffice to demonstrate effectiveness of a cholera vaccine in persons not previously exposed to cholera provided that studies were adequate,well-controlled and conducted under the provisions of GCP[12,13].

9. Other Relevant Regulatory Issues

Recommended to Grant Priority Review and Tropical Disease Priority Review Voucher

Priority Review

PaxVax requested priority review for this BLA, based on the premise that the protective effectiveness of VAXCHORA against moderate to severe diarrhea caused by *V. cholerae* serogroup O1 is high, and VAXCHORA offers a significant improvement in the safety and effectiveness of current prevention strategies recommended for US travelers to cholera-affected areas. The BLA was granted priority review because 1) VAXCHORA prevents cholera, which is a serious disease and, 2) if licensed, VAXCHORA would be a significant improvement in effectiveness for prevention of cholera for U.S. travelers to cholera–affected areas.

Tropical Disease Priority Review Voucher

In the BLA, PaxVax stated that their application for VAXCHORA was eligible for a Tropical Disease Priority Review Voucher upon approval, because:

1. VAXCHORA is intended for the prevention of a listed tropical disease, namely Cholera,
2. The application is submitted under section 351 (a) of the PHS Act,
3. VAXCHORA (the genetically modified CVD 103-HgR vaccine strain) is a new molecular entity and does not contain an active ingredient (including any ester or salt of the active ingredient) that has been approved by the FDA in any other application under Sectdion 505(b)(1) of the Act of section 351 of the PHS Act.
4. VAXCHORA for priority review.

VAXCHORA meets all the criteria for a Tropical Disease Priority Review Voucher described in the CBER Guidance document available at (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM080599.pdf).

Therefore, PaxVax's BLA is granted a Tropical Disease Priority Review Voucher.

10. Labeling

The proprietary name, VAXCHORA, was reviewed by the Advertising and Promotional Labeling Branch on December 15, 2015, and found acceptable. CBER communicated this decision to PaxVax on December 21, 2015.

The carton and container labels were reviewed. All issues, including required revisions, were resolved after exchange of information and discussions with PaxVax.

The prescribing information (PI) was reviewed and specific comments on the labeling were provided by CBER to PaxVax, who made the requested revisions. Some of the issues raised during the review of the VAXCHORA PI were: 1) indication for use in U.S. residents traveling to cholera affected areas, 2) lack of data demonstrating effectiveness of VAXCHORA in persons who may have pre-existing immunity due to previous exposure to *V. cholerae* or receipt of a cholera vaccine, 3) use of purified bottled water to reconstitute the lyophilized VAXCHORA powder, 4) VAXCHORA should be reconstituted within 15 minutes from its removal from the freezer, 5) anti-malaria drug Chloroquine should not be administered within 10 days of vaccination with VAXCHORA and 5) modification of the description of the mechanism of action section. All issues were satisfactorily resolved.

11. Recommendations and Risk/ Benefit Assessment

a. Recommended Regulatory Action

The committee recommends approval of the BLA.

b. Risk/ Benefit Assessment

Based on the data submitted by PaxVax to support the safety and effectiveness of VAXCHORA that have been presented and discussed in this document, as well as the serious illness associated with cholera disease, the review committee is in agreement that the risk/benefit profile for VAXCHORA is favorable and supports approval of this BLA.

c. Recommendation for Postmarketing Risk Management Activities

At this time, we recommend that the applicant should conduct routine surveillance reported in accordance with 21 CFR 600.80.

d. Recommendation for Postmarketing Activities

Post-marketing Requirements

- Studies in children ≥ 2 years to <18 years of age will be conducted to fulfill PREA requirements.

  Final protocol submission: December 31, 2016
  Study completion: December 31, 2018
  Final report submission: June 30, 2019

Post-marketing Commitments

- PaxVax committed (in accordance with 21 CFR 601.70) to establish a pregnancy registry for VAXCHORA in the U.S. to prospectively collect data on spontaneously reported exposures to VAXCHORA occurring within 28 days prior to the last menstrual period or at any time during pregnancy. The applicant will submit annual reports as well as a 5-year summary report, after which PaxVax will continue enrolling patients in the registry and submitting annual reports pending CBER review of the reports and determination that the registry can be discontinued.

  Final protocol submission: July 1, 2016
  Study completion: September 1, 2021
  Final report submission: September 1, 2022

12. References

1. WHO (2014a) Weekly Epidemiological Report, Cholera, 2013, No. 31, 2014 (89) 345–356.
2. Richie, E., Punjabi, N. H., Sidharta, Y., Peetosutan, K., Sukandar, M., Wasserman, S. S., & Simanjuntak, C. H. (2000). Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera-endemic area. Vaccine, 18(22), 2399-2410.
3. Tacket, C.O., Losonsky, G., Nataro, J.P., Cryz, S.J., Edelman, R., Kaper, J.B., Levine, M.M. (1992). Onset and duration of protective immunity in challenged volunteers after vaccination with live oral cholera vaccine CVD 103-HgR. Journal of Infectious Diseases 166: 837-841.
4. Tacket, C. O., Cohen, M. B., Wasserman, S. S., Losonsky, G., Livio, S., Kotloff, K., ... & Levine, M. M. (1999). Randomized, double-blind, placebo-controlled, multicentered trial of the efficacy of a single dose of live oral cholera vaccine CVD 103-HgR in preventing cholera following challenge with *Vibrio cholerae* O1 El tor Inaba three months after vaccination. Infection and immunity, 67(12), 6341-6345.
5. Richardson SH. In: Wachsmuth IK, Blake PA, Olsvik O, eds. Chapter 14. Vibrio cholera and Cholera: Molecular to Global Perspective. 1994. Washington, DC: American Society for Microbiology.
6. Levine, M. M., Kaper, J. B., Black, R. E., & Clements, M. L. (1983). New knowledge on pathogenesis of bacterial enteric infections as applied to vaccine development. Microbiological reviews, 47(4), 510.
7. Levine, M. M., & Kaper, J. B. (1993). Live oral vaccines against cholera: an update. Vaccine, 11(2), 207-212.
8. Glass, R. I., Becker, S., Huq, M. I., Stoll, B. J., Khan, M. U., Merson, M. H., ... & Black, R. E. (1982). Endemic cholera in rural Bangladesh, 1966–1980. American journal of epidemiology, 116(6), 959-970.
9. Holmgren, J & Kaper, JB (2010). Oral cholera vaccines. In New Generation Vaccines (pp 506 514) New York; NY: Informa Healthcare USA, Inc.
10. Glass, R. I., Svennerholm, A. M., Khan, M. R., Huda, S., Huq, M. I., & Holmgren, J. (1985a). Seroepidemiological studies of EI Tor cholera in Bangladesh: association of serum antibody levels with protection. Journal of infectious diseases, 151(2), 236-242.
11. Kollaritsch, H., Cryz, S. J., Lang, A. B., Herzog, C., Que, J. U., & Wiedermann, G. (2000). Local and systemic immune responses to combined *Vibrio cholerae* CVD103-HgR and *Salmonella typhi* ty21a live oral vaccines after primary immunization and reimmunization. Vaccine, 18(26), 3031-3039.
12. Vaccines and Related Biological Products Advisory Committee meeting transcript, January 26, 1993. http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3422t1.pdf
13. Vaccines and Related Biological Products Advisory Committee meeting transcript, May 26-27, 1998. http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3422t2a.pdf

Concurrence Page

Application Type and Number: BLA _____125597/0_____

COMMUNICATION TYPE:

History:
Prepared by: Goutam Sen
Reviewed by: Jon Daugherty, Jeff Roberts, Loris McVittie, Wellington Sun, Karen Farizo, Marion Gruber, Mary Malarkey, Roshan Ramanathan

Concurrence:

Office/Division	**Name/Signature**
DVRPA/OVRR	Christina Houck/Jon Daugherty
DVRPA/OVRR	Goutam Sen
OVRR	Marion Gruber
OCBQ	Mary Malarkey